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10/601,634	06/24/2003	Mikhail Markovich Cusyatiner	239410US0	1117

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EXAMINER	
RAMIREZ, DELIA M	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 09/11/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/601,634	CUSYATINER ET AL.	
	Examiner	Art Unit	
	Delia M. Ramirez	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 June 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-9* is/are pending in the application.

4a) Of the above claim(s) *6 and 7* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-5,8 and 9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 June 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Application

Claims 1, 3-9 are pending.

Applicant's amendment of claims 1, 3-4, 6, cancellation of claim 2, and addition of new claims 8-9 as submitted in a communication filed on 6/20/2006 is acknowledged.

This application contains claims 6-7 drawn to an invention non-elected with traverse in a communication filed on 12/29/2005. A complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

New claims 8-9 are directed to the elected invention. Claims 1, 3-5, 8-9 are at issue and are being examined herein.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Specification

1. The specification was previously objected to due to the presence of several grammatical/typographical errors. In view of Applicant's amendments to the specification, this objection is hereby withdrawn.

2. The specification as amended in the response filed on 6/20/2006 is objected to for the following reasons. On top of page 2 of the response, the first paragraph amended by Applicant does not appear to correspond to the paragraph starting on page 16, line 11 as indicated. Instead, that paragraph corresponds to page 7, line 6-page 8, line 2. Appropriate correction is required.

Claim Objections

3. Claim 3 is objected to due to the recitation of "a copy number of said tyrB gene". For consistency with commonly used claim language, it is suggested the term "a copy number" be replaced with "the copy number". Appropriate correction is required.

Claim Rejections - 35 USC § 101

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. Claims 1-3 were rejected under 35 U.S.C. 101 because the claimed invention was directed to non-statutory subject matter. In view of Applicant's amendment of claim 1 which now recites the term "isolated", and in view of Applicant's cancellation of claim 2, this rejection is hereby withdrawn.

Claim Rejections - 35 USC § 112, First Paragraph

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. Claims 1, 3-5 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been discussed at length in the Non Final action mailed on 3/23/2006 and it is maintained for the reasons of record and those set forth below.

8. Applicant argues that the claims have been amended to address previous criticisms by the Examiner regarding the broad genus of ilvE genes, genes encoding aromatic acid aminotransferases, and modifications required by the claims. In view of these amendments, Applicant argues that the claimed

invention is fully described and enabled by the specification. Applicant submits that inactivation of the ilvE gene can be performed not only by deletion mutations, but also by site-directed mutagenesis, homologous recombination, and insertion mutagenesis. In addition, Applicant contends that methods for decreasing the activity of the protein encoded by the ilvE gene include modifications to the expression regulation sequence of the ilvE gene besides modifications to the protein coding sequence of the ilvE gene. With regard to the tyrB gene, applicant argues that the activity of the tyrB gene product can also be achieved by placing the gene under the control of a potent promoter. Applicant also submits that since the *E. coli* ilvE gene and the protein encoded by it have been disclosed in GenBank and the accession numbers have been disclosed in the specification, it is not necessary to recite information already known in the art. Thus, Applicant concludes that the claimed invention complies with 35 USC 112, first paragraph.

9. Applicant's arguments have been fully considered but are not deemed persuasive to overcome all the grounds of rejection previously applied with regard to written description. The Examiner acknowledges the amendments made to the claims and agrees that the invention is now adequately described with regard to the *E. coli* tyrB gene and increased activity of the corresponding protein product by increasing the copy number of said gene, or by placing the gene under the control of a potent promoter, as described on page 11, lines 1-4 of the specification. The Examiner also acknowledges that the *E. coli* ilvE gene and its protein product (transaminase) have been disclosed in the prior art. However, claim 1, from which claims 3-5 depend, requires an *Escherichia* cell wherein (1) the inactivation of the ilvE gene in that cell is not limited to mutations made solely to the coding region of the ilvE gene by methods such as deletion, homologous recombination, or insertion mutagenesis, or (2) decreasing the activity of the protein encoded by the endogenous ilvE gene is not limited to mutations made to that protein which would render the protein enzymatically inactive. It is noted that the specification on page 7, lines 6-10 defines the term "inactivation of ilvE gene" as encompassing a gene which is modified such

that it is unable to express any enzyme. As previously indicated in the Non Final action mailed on 3/23/2006, inactivation of a gene can also be achieved by other methods such as using transcription inhibitors/regulators or modifications in the regulatory region of the gene which would block transcription (i.e., expression of the enzyme). These transcription inhibitors/modulators can be chemical compounds or the products of genes which are totally unknown. While it is agreed that methods such as homologous recombination or insertion mutagenesis are well known and can be used to mutate the ilvE gene such that its protein product is no longer enzymatically active, the claims encompass modifications in other genes or the presence of compounds of unknown nature that would lead to the inactivation of that gene, none of which defined in the specification. With regard to decreasing the activity of the protein product of the ilvE gene, it is noted that the specification on page 8, lines 3-7 defines the term "decreasing activity of the protein coded by the ilvE gene" as encompassing any modification which would result in the enzymatic activity per cell reduced. While deletion mutations in the coding region of the ilvE gene which would result in the gene product to be enzymatically inactive are described, decreasing the activity of the protein coded by the ilvE gene also encompasses (1) mutations within the coding region which would reduce the enzymatic activity to different levels besides total inactivation (e.g., 10%, 20%, 30% and so forth of the wild-type enzymatic activity), and (2) the presence of inhibitors of that enzymatic activity that can be chemical compounds as well as the products of genes that are completely unknown. It is noted that the claims require a specific percent of L-leucine with respect to L-valine, L-isoleucine and L-homoleucine. While the specification discloses that an inactivating deletion of the ilvE gene in *E. coli* would result in the amount of L-valine, L-isoleucine and L-homoleucine to be less than 1% that of L-leucine, the specification fails to disclose how much of the enzymatic activity of the ilvE gene product has to be reduced (in addition to elimination of the enzymatic activity) to obtain the "less than 1%" limitation recited, and which modifications have to be made to obtain the level of reduction in enzymatic activity that would result in the amount of L-valine, L-isoleucine and L-homoleucine to be less than 1% that of L-

leucine. For example, is a 10% reduction in enzymatic activity sufficient to obtain the less than 1% amount of L-valine, L-isoleucine and L-homoleucine required by the claims? If so, which modifications would result in a 10% decrease in enzymatic activity? Clearly, the claims encompass modifications not adequately described by the teachings of the specification. Thus, contrary to Applicant's assertions, one of skill in the art cannot reasonably conclude that the claimed invention meets the written description requirements as set forth in 35 USC 112, first paragraph.

10. New claims 8-9 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is necessitated by amendment.

The invention appears to require a novel bacterial strain. Since the bacterial strain is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The claimed bacterial strain has not been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. 112 may be satisfied by a deposit of the bacterial strain. The specification does not disclose a repeatable process to obtain the bacterial strain and it is not apparent if the bacterial strain is readily available to the public. Accordingly, it is deemed that a deposit of this bacterial strain should have been made in accordance with 37 CFR 1.801-1.809.

It is noted that Applicant has deposited the bacterial strain (page 16, last sentence-page 17, lines 1-2) but there is no indication in the specification as to public availability. If the deposit was made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific bacterial strain has been deposited under the Budapest Treaty and that the bacterial strain will be available to the public under the conditions specified in 37 CFR 1.808, would satisfy the deposit requirement made herein.

If the deposit has not been made under the Budapest treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, Applicant may provide assurance or compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

a. during the pendency of this application , access to the invention will be afforded to the Commissioner upon request;

b. upon granting of the patent the strain will be available to the public under the conditions specified in 37 CFR 1.808;

c. the deposit will be maintained in a public repository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer; and

d. the deposit will be replaced if it should ever become unviable.

11. Claims 1, 3-5 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an *Escherichia* cell wherein said cell produces L-leucine, L-valine, L-isoleucine and L-homoleucine, wherein the amount of L-valine, L-isoleucine and L-homoleucine produced is less than 1% the amount of L-leucine produced due to an inactivating deletion in the ilvE gene of said *Escherichia* cell, wherein the protein activity of the *E. coli* tyrB gene product is increased in said *Escherichia* cell by (1) transforming said *Escherichia* cell with a DNA comprising the *E. coli* tyrB gene and increasing the copy number of the *E. coli* tyrB gene, or (2) placing the *E. coli* tyrB gene under the control of a potent promoter, does not reasonably provide enablement for an *Escherichia* cell that produces L-leucine, L-valine, L-isoleucine and L-homoleucine, wherein the amount of L-valine, L-isoleucine and L-homoleucine produced is less than 1% the amount of L-leucine produced, wherein the ilvE gene in said *Escherichia* cell is inactivated by any method, or the activity of the gene product of the ilvE gene is decreased by any method. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

commensurate in scope with these claims. This rejection has been discussed at length in the Non Final action mailed on 3/23/2006 and it is maintained for the reasons of record and those set forth below.

12. Applicant's arguments with regard to the enablement rejection are the same as those already summarized above regarding the written description rejection.

13. Applicant's arguments have been fully considered but are not deemed persuasive to overcome all the grounds of rejection previously applied with regard to enablement. It is reiterated herein that the Examiner acknowledges (1) the amendments made to the claims, (2) adequate description of the *E. coli* tyrB gene and increased activity of its gene product by increasing the copy number of said gene, or by placing the gene under the control of a potent promoter, (3) disclosure of the *E. coli* ilvE gene and its protein product (transaminase), and (4) the specification's disclosure of an inactivating deletion in the *E. coli* ilvE gene that results in an *E. coli* cell to produce L-isoleucine, L-valine, and L-homoleucine in an amount which is less than 1% that of L-leucine. However, as previously indicated, (1) the inactivation of the ilvE gene in the *Escherichia* cell is not limited to mutations made solely to the coding region of the ilvE gene by methods such as deletion, homologous recombination, or insertion mutagenesis, and (2) decreasing the activity of the protein encoded by the ilvE gene is not limited to mutations made to that protein which would render the protein enzymatically inactive. While inactivation of a gene can be achieved by using transcription inhibitors/regulators or modifications in the regulatory region of the gene which would block transcription (i.e., expression of the enzyme), the specification is completely silent with regard to the identity of the transcription inhibitors/modulators that can block transcription. As indicated above, these inhibitors/modulators can be chemical compounds or the products of genes which are totally unknown. Furthermore, the specification is completely silent with regard to the structural modifications in the regulatory region of that gene which would block transcription. Similarly, while decreasing the activity of the protein product of the ilvE gene encompasses (1) mutations within the coding region which would reduce the enzymatic activity to different levels besides total inactivation, and

(2) the presence of inhibitors of that enzymatic activity, the specification is completely silent with regard to the levels of reduction in protein activity required to achieve the required "less than 1%" limitation recited in the claims, how to achieve those levels of reduction in protein activity, or the identity of inhibitors of enzymatic activity. As stated in the Non Final action mailed on 3/23/2006, it is not routine in the art to screen by trial and error for (1) any modification which would result in inactivation of the ilvE gene in any *Escherichia* cell, (2) any transcription inhibitor/modulator of the ilvE gene in an *Escherichia* cell, (3) an essentially infinite number of mutations in the regulatory region of the ilvE gene or in the coding region of such gene to determine which ones result in reduced enzymatic activity or decreased amount of the ilvE gene product per cell sufficient to achieve the "less than 1%" limitation, or (4) any enzymatic activity inhibitor of the ilvE gene product. In the absence of some knowledge or guidance as to (1) which structural modifications are required to obtain the desired effect, and (2) the structure of molecules capable of blocking transcription of the ilvE gene or capable of inhibiting the enzymatic activity of the ilvE gene product, one of skill in the art would have to go through the burden of undue experimentation to enable the full scope of the claimed invention. Thus, contrary to applicant's assertions, the claimed invention is not fully enabled by the teachings of the specification.

Claim Rejections - 35 USC § 102

14. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

15. Claim 1 remains rejected under 35 U.S.C. 102(b) as being anticipated by Gelfand et al. (J. Bacteriol. 130(1):429-440; cited in the IDS). This rejection has been discussed at length in the Non Final action mailed on 3/23/2006 and is maintained for the reasons of record and those set forth below.

16. Applicant traverses the instant rejection on the grounds that Gelfand et al. fail to suggest the L-valine, L-isoleucine and L-homoleucine content recited in the claim (i.e., less than 1% that of L-leucine).

Applicant argues that while it is the Examiner's position that this limitation is inherent, the Examiner has failed to provide a reasonable basis in fact and/or technical reasoning to support a determination of inherency. According to Applicant, the Examiner has overlooked the genotype description of Table 1 of Gelfand et al., where it is shown that strain DG31 is also transduced with $tyrA^+$ and strain DG34 is transduced with aspC13 and ilvEl2. Applicant argues that since the doctrine of inherency is based on certainties and in view of the uncertainty with regard to how the presence of ilvE12 and aspC13 would affect the production of L-valine, L-isoleucine and L-homoleucine, the present invention is not anticipated by Gelfand et al.

17. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the rejection. Claim 1 as amended is now directed in part to an *Escherichia* cell which produces L-valine, L-isoleucine, and L-homoleucine at an amount which is less than 1% that of L-leucine due to inactivation of the ilvE gene. As previously indicated in the Non Final action, Gelfand et al. teach two mutant *E. coli* cells which can synthesize leucine, wherein the ilvE gene has an inactivating deletion, strain DG31 ($ilvE^-$ $tyrB^+$) and strain DG34 ($ilvE^-$ $tyrB^+$), and the endogenous tyrB gene is functional (page 436, right column, Leucine biosynthesis by the tyrB aminotransferase, page 437 left column). Gelfand et al. also teach that the presence of the tyrB gene product (aromatic amino acid aminotransferase) allows leucine to be synthesized (DG31 and DG34 can grow in the absence of leucine) whereas its absence results in not enough leucine to sustain growth (strain DG27 ($ilvE^-$ $tyrB^-$) has an absolute requirement for leucine).

The Examiner acknowledges that Gelfand et al. do not explicitly state that the amount of L-valine, L-isoleucine and L-homoleucine produced by their strains is less than 1% that of L-leucine. However, as previously indicated in the Non Final action mailed on 3/23/2006, the Examiner based her argument of inherency on Applicant's own disclosure where it is indicated that *E. coli* strain 505, which has an inactivating deletion in the ilvE gene, produces L-valine, L-isoleucine and L-homoleucine at an amount which is less than 1% that of L-leucine (Table 1, second entry). It should be noted that the

specification does not provide the genetic background of *E. coli* strain 505, nor does it indicate that the presence or absence of other genes in *E. coli* strain 505 would interfere with the observed effect on L-leucine production with respect to L-isoleucine, L-valine and L-homoleucine (i.e., no indication that a specific genetic background should be present in addition to a deletion in the ilvE gene). Thus, based on Applicant's disclosure, it has been presumed that in general, a deletion in the ilvE gene of an *E. coli* cell would result in L-isoleucine, L-valine and L-homoleucine to be produced at an amount which is less than 1% the amount of L-leucine. *E. coli* strain 505 (page 15, Example 1, first sentence) and Gelfand's strains are all *E. coli* K-12 derivatives (page 429, right column, Materials and Methods, Bacterial strains). Furthermore, while the Examiner agrees that Gelfand's strain DG31 is also $tyrA^+$, it is noted that *E. coli* strain 505 has not been disclosed as $tyrA^-$, thus it is assumed that *E. coli* strain 505 is also $tyrA^+$. Unless *E. coli* strain 505 is $tyrA^-$, both Gelfand's *E. coli* strain DG31 and Applicant's *E. coli* strain 505 would have an $ilvE^-$ $tyrB^+$ $tyrA^+$ background. As such, based on the teachings of the specification, one of skill in the art would expect *E. coli* strain DG31 to produce L-isoleucine, L-valine and L-homoleucine at an amount which is less than 1% that of L-leucine.

With regard to strain DG34, while it is agreed that the genetic background of that strain also includes aspC13 and ilvE12, it is noted that ilvE12 is a deletion in the ilvE gene (page 432, left column, Introduction of $ilvE^-$), and aspC13 is assumed to be an inactivating deletion in the aspC gene in view of the fact that Gelfand et al. teach that DG34 lacks aspartate aminotransferase activity (page 436, right column, Substrate specificity of the aromatic amino acid aminotransferase; aspC encodes an asparate aminotransferase). Thus, unless the location of the deletion in the ilvE gene would influence the amount of L-leucine produced with respect to L-valine, L-isoleucine and L-homoleucine, the only obvious difference between strain DG34 and strain 505 is the fact that DG34 is $aspC^-$. Vartak et al. (J. Bacteriol. 173(12):3864-3871, 1991) discloses that in wild type *E. coli* K-12, the aspC gene product (aspartate aminotransferase, TrA) does not catalyze physiologically detectable leucine biosynthesis when present in

a single copy in the chromosome (page 3864, left column, second paragraph; TrA). Thus, it appears that the presence or absence of chromosomal aspC in *E. coli* K12 does not affect the synthesis of L-leucine. Gelfand et al. also teach that strain DG34 can grow in L-leucine and cannot grow in the absence of L-isoleucine (Table 5, page 438), thus indicating that while L-leucine is being synthesized, almost no L-isoleucine is produced by this strain. There is no evidence to suggest that the aspC gene product would have an effect on the synthesis of L-valine or L-homoleucine. Thus, absent evidence to the contrary, and in view of applicant's disclosure which appear to suggest that in *E. coli* an inactivating deletion in the ilvE gene would result in the amount of L-valine, L-isoleucine and L-homoleucine produced to be less than 1% that of L-leucine, one of skill in the art would reasonably conclude that strain DG34 would also produce L-valine, L-isoleucine, and L-homoleucine at an amount which is less than 1% that of L-leucine. Even if the argument is made that the effect of a deletion in the aspC gene on the synthesis of L-valine and L-homoleucine is unknown such that one could not reasonably conclude that *E. coli* strain DG34 would meet the limitations recited in the claim, Gelfand's additional *E. coli* strain, DG31, would still anticipate the instant claim as written for the reasons stated above.

Claim Rejections - 35 USC § 103

18. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

19. Claims 3-5 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Gelfand et al. (J. Bacteriol. 130(1):429-440; cited in the IDS). This rejection has been discussed at length in the Non Final action mailed on 3/23/2006 and is maintained for the reasons of record and those set forth below.

20. Applicant argues that the present invention is not obvious over Gelfand et al. because the strains of Gelfand et al. do not produce L-valine, L-isoleucine and L-homoleucine at an amount which is less than 1% that of L-leucine. Applicant also argues that this reference does not teach how to produce a

bacterium that synthesizes L-valine, L-isoleucine and L-homoleucine at an amount which is less than 1% that of L-leucine, and asserts that the instant reference would fail to render the claimed invention obvious even if the skilled artisan were to transform the bacterium disclosed therein with the tyrB gene to overexpress said tyrB gene.

21. Applicant's arguments have been fully considered but are not deemed persuasive to overcome the instant rejection. Claims 3-5 are directed in part to the *Escherichia* cell of claim 1 as described above, wherein the cell is transformed with a multicopy vector which contains the *E. coli* tyrB gene to increase the enzymatic activity of the gene product of the *E. coli* tyrB gene. For the reasons extensively discussed above, while one of skill in the art would reasonably conclude that both *E. coli* strains disclosed by Gelfand et al. anticipate claim 1, even if the argument is made that the effect of a deletion in the aspC gene on the synthesis of L-valine and L-homoleucine is unknown such that *E. coli* strain DG34 would not meet the limitations recited in claim 1, *E. coli* strain DG31 would still anticipate claim 1 in view of the fact that both *E. coli* strain 505 and *E. coli* strain DG31 have an $ilvE^-$ $tyrB^+$ $tyrA^+$ background. As indicated in the Non Final action, it would have been obvious to transform the *E. coli* mutants of Gelfand et al. with a multicopy vector which contains the *E. coli* tyrB gene to increase the enzymatic activity of the gene product of the *E. coli* tyrB gene in view of the fact that Gelfand et al. teach that those strains which have an intact tyrB gene are capable of producing L-leucine (page 436, right column, Leucine biosynthesis by the tyrB aminotransferase) when ilvE gene is inactivated. It is reiterated herein that a person of ordinary skill in the art is motivated to transform the *E. coli* mutants of Gelfand et al. with a multicopy vector comprising DNA encoding the *E. coli* tyrB gene product to (1) produce L-leucine, which is an amino acid of industrial importance, while reducing the amount of other amino acids which can be considered contaminants, and (2) to further characterize the leucine/valine/isoleucine biosynthetic pathway. *E. coli* is a well known microbial producer of amino acids. There is a reasonable expectation of success at transforming the *E. coli* mutants of Gelfand et al. with a multicopy vector comprising the *E.*

coli tyrB gene since transformation of *E. coli* cells with multicopy number vectors is well known and widely used in the art. Furthermore, there is a reasonable expectation of success at obtaining L-leucine in view of Gelfand's teaching regarding the ability of strains having the tyrB gene intact to produce L-leucine when the ilvE gene is disrupted. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Conclusion

22. No claim is in condition for allowance.

23. Applicant's amendment adding new claims 8-9 necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

24. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

25. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 8:30 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Ponnathapura Achutamurthy can be reached on (571) 272-0928. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Delia M. Ramirez, Ph.D.
Patent Examiner
Art Unit 1652

DR
August 28, 2006